REMARKS

Claims 1, 3, 5-15, 17-23 and 42-56 are currently pending in this application. Applicants acknowledge with appreciation the Examiner's withdrawal of various objections and rejections and the Allowance of claim 42 as detailed in the November 4, 2003 Final Office Action. Applicants respectfully request that the Examiner enter the amendments presented herein in order to place the claims in better condition for Allowance or Appeal.

Claims 1 and 3 have been amended to recite features formerly recited in claims 2 and 4, respectively. Claims 2 and 4 have been canceled herein.

Claim 22 has been amended to recite features of claim 23. Claim 23 has been canceled.

None of the amendments presented herein constitute new matter. Applicants reserve the right to pursue canceled subject matter in applications claiming priority to the instant application. Applicants address below the outstanding objections and rejections.

THE REJECTIONS

35 U.S.C. § 112, first paragraph

Claims 1-15, 17-21, and 50-56 stand rejected under 35 U.S.C. § 112, first paragraph. Additionally, claims 22, 23 and 43-49 stand similarly rejected. Specifically, the Examiner maintains his contention that the Specification only enables **neuronal** cells that (1) express GFAP and nestin, (2) express the striatal markers DLX-1 and/or Meis2, and (3) do not express cortical markers (i.e. PAX6). The Examiner sets forth a similar argument in rejecting the related method claims. In further support of the rejections, the Examiner again cites Kalyani et al. and U.S. 6,040,180. Applicants traverse these rejections based on the Specification as originally filed and the arguments presented herein.

The subject of the invention is NS4 cells. NS4 cells are **undifferentiated** neural cells which can be induced, for example, to proliferate (as described in the Specification on page 6, lines 16-18). As described in the Specification and recited in the pending claims, NS4 cells express GFAP and nestin (page 6, line 20). In addition to their ability to proliferate, these cells

can be differentiated into neurons or glial cells (as described in the Specification on page 13, lines 22-23, and in Figure 1).

DLX-1 and Meis2 are markers expressed by differentiating neurons (page 28, line 28). They are, however, not expressed by undifferentiated neural cells during proliferation (i.e. proliferating NS4 cells). In fact, the Specification makes clear in many places that NS4 cells need not express DLX and Meis2. For example, the Specification states that only **some** cells express transcription factors typical of differentiating neurons (DLX and Meis2) after differentiation (Example 1, page 28, lines 25-27). Additionally, Example 4 describes the immunoreactivity of proliferating NS4 cells, yet any mention of DLX1 and/or MEIS2 expression is notably absent (i.e., page 33, line 20 to page 34, line 7). In that respect, Example 5 (which is directed towards differentiation of NS4 cells) is consistent in stating that DLX1 and MEIS2 expression is seen **after differentiation into neurons** (page 35, lines 6-8). Finally, Example 5 (page 35, lines 6-8) teaches that the absence of expression of cortical markers, specifically PAX6, is indicative of **differentiated neurons**.

As the Specification makes clear, striatal markers are only expressed after differentiation into neurons (and not in all cells) and the absence of PAX6 expression is also correlated to differentiated neurons. Thus, because the Specification describes proliferating and/or undifferentiated NS4 cells (and methods for making them), the specification does provide enablement for NS4 cells expressing GFAP and nestin (i.e., without the further limitation). Accordingly, the pending claims are commensurate in scope with the teaching of the Specification (i.e. claims 44 and 45 recite that the striatal markers are expressed in **differentiated neuronal** cells and claims 46 and 46 recite that the **differentiated neuronal** cells obtainable from NS4 cells do not express cortical markers).

Kalyani et al. (1998)

Kalyani et al. (1998), according to the Examiner, teaches that neuronal restricted precursor cultures are notoriously heterogenous and respond to a variety of extracellular signals (i.e. the reference demonstrates "the obstacles and difficulty in using stem cells pursuant to

MPEP §2164.03"). Applicants traverse this contention.

Kalyani et al teaches that the specific E-NCAM expressing cells (which were derived from the spinal chord) are self-renewing and can generate multiple neuronal phenotypes (page 7867, first col., last paragraph). Applicants fail to see how this translates into obstacles and difficulties in general in culturing and differentiating neural cells. It may be true that Kalyani et al (page 7866, passage cited by the examiner) speculate that the specific effect of BMP-2 will depend on age and on which precursor cells are present in a mixed population of cells. It should be noted that this statement is not based on observed facts but is merely part of the Discussion section of the reference. The alleged heterogeneity of the culture they used did not prevent Kalyani et al. from concluding that "BMP-2 acts to promote neuronal differentiation from neuronal-restricted precursors". Further, the Kalyani et al. reference does not express doubts that their teachings can be applied to other situations. In the previous Office Action, the Examiner referred to Figure 6 and concluded that even cells taken from an anatomically defined area respond differently to proliferation-inducing factors. Applicants traverse. Figure 6 demonstrates that FGF (a mitogen) promotes proliferation, that Shh promotes proliferation compared to NT-3, and that BMP-2 promotes differentiation. Applicants fail to see how Figure 6 teaches any kind of unpredictability and obstacles with respect to cells. FGF is the only mitogen described – consequently, no unpredictability with respect to mitogens can be derived from the figure.

The examiner also contends that Kalyani et al. teaches that cloned cultures vary in their responsiveness to neurotransmitters. Whether Kalyani et al. actually teaches this is irrelevant to the instantly claimed invention, as the responsiveness to neurotransmitters is not the subject of the present invention. In conclusion, Kalyani et al. does not demonstrate general unpredictability in the art. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw his use of this reference.

US 6,040,180 (Johe)

Finally, the examiner maintains his contention that US 6,040,180 (Johe) is proof of unpredictability in the art of culturing and differentiating CNS stem cells. Applicants traverse.

As an initial matter, the expression quoted by the examiner (column 7) should be interpreted with care since the very purpose of the statement was to argue the patentability of the methods of Johe. Johe tries to argue that the (then) prior art had difficulties but that the methods disclosed in the application had solved these problems.

In the actual data presented in the Johe patent, there is no mention of unpredictability even though the reference deals with stem cells isolated from many different locations within the CNS (column 8, lines 10-14), which after proliferation can be "differentiated into neurons, oligodendrocytes, and astrocytes with **control** and efficacy" (col. 14, lines 42-45, emphasis added). Such statements are certainly not consistent with a general unpredictability in the art. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this reference.

CONCLUSION

Applicants respectfully requests that the Examiner enter the requested amendments, consider the foregoing remarks and withdraw the outstanding rejections. Should the Examiner feel that a telephone conference would expedite allowance of the pending claims, he is invited to call the undersigned.

Respectfully submitted,

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